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Freedom of Information Summary

Carprofen® Chewable Tablets (carprofen)

NADA 141-111

Pfizer Inc.
235 East 42 Street
New York, NY 10017

FOIS 1

Table of Contents

Freedom of Information Summary

I. General Information

NADA Number:	NADA 141-111
Sponsor:	Pfizer Inc. 235 East 42nd Street New York, New York 10017
Generic Name:	Carprofen
Trade Name:	Rimadyl® chewable tablets
Marketing Status:	Prescription

II. Indications for Use:

Rimadyl® chewable tablets are indicated for the relief of pain and inflammation associated with osteoarthritis in dogs.

III. Dosage Form, Route of Administration and Recommended Dosage:

A. Dosage Form: Rimadyl® chewable tablets are available as 25 mg, 75 mg, and 100 mg scored tablets.

B. Route of Administration: Oral

C. Recommended Dosage: The recommended dosage for oral administration to dogs is 1 mg/lb of body weight twice daily. Rimadyl® chewable tablets are scored and the dosage should be calculated in half-tablet increments. Tablets can be halved by placing the tablet on a hard surface and pressing down on both sides of the score. Rimadyl® chewable tablets are palatable and willingly consumed by most dogs. Tablets may be fed free choice or placed on food. Care should be taken to ensure that the dog consumes the complete dose.

IV. Effectiveness:

A. Reference is made to information contained in the original FOI Summary for NADA 141-053.

B. Studies

1. Relative Bioavailability of a single 1.0 mg/lb and 3.0 mg/lb dose of orally administered carprofen in caplet and chewable dose forms in dogs (Study No. 2567A-60-97-106).

   a. Type of Study: Plasma Level Bioavailability

   b. Investigator: Dr. Elizabeth I. Evans
   Midwest Research Institute (MRI)
   425 Volker Boulevard
   Kansas City, Missouri

   c. General Design:

      i. Purpose: The objective of the study was to demonstrate comparable relative bioavailability between single doses of 25 mg and 75 mg of carprofen in a caplet formulation and single doses of 25 mg and 75 mg of carprofen in a chewable tablet formulation.

      ii. Test Animals: Sixteen (16) healthy male Beagle dogs approximately 9 months of age and ranging in weight from 20.3-25.0 lb participated in the study.

      iii. Control Group: Rimadyl® caplets (25 mg and 75 mg)

      iv. Dosage Form: Rimadyl® chewable tablets (25 mg and 75 mg). The chewable tablets administered were the same as the proposed market formulation.

      v. Route of Administration: Oral

      vi. Dose: Carprofen 1.0 and 3.0 mg/lb as a single dose.

      vii. Study Design: The study was performed in two phases. Phase I was a two period, two treatment cross-over experimental design, with each replicate being separated by a washout period of 10 days. Study dogs were randomly assigned to two groups (A or B) of eight dogs each. On Day 0, Group A dogs received 1.0 mg/lb of carprofen as a 25 mg caplet; Group B dogs received 1.0 mg/lb of carprofen as a 25 mg chewable tablet. On Day 10, Group A dogs received 1.0 mg/lb of carprofen as a 25 mg chewable tablet; Group B dogs received 1.0 mg/lb of carprofen as a 25 mg caplet. Phase II was a two treatment parallel experimental design with dosing after an 11 day washout period. Study dogs were again randomly assigned to one of two groups (C or D) of eight dogs each. On Day 21, Group C dogs

received 3.0 mg/lb of carprofen as a 75 mg caplet; Group D dogs received 3.0 mg/lb of carprofen as a 75 mg chewable tablet.

viii. Parameters measured: For both study phases, plasma samples were collected for carprofen analysis prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours following dosing. Plasma samples were assayed for carprofen using a validated HPLC method.

d. Results: Means and confidence interval boundary information for the pharmacokinetic variables ($AUC_{0\text{-}LOQ}$, C_{max}, and T_{max}) are summarized in Tables 1 and 2.

Table 1. Means and Confidence Intervals: 25 mg Carprofen Caplet and 25 mg Carprofen Chewable Tablet (Phase I, 1.0 mg/lb Dosing)

Pharmacokinetic Variable	Mean[1]	90% Confidence Interval[2] Lower Bound (%)	Upper Bound (%)
$AUC_{0\text{-}LOQ}$ (μg/mL●hr)			
Caplet	125.2		
Chewable Tablet	119.6	-12.7	4.6
C_{max} (μg/mL)			
Caplet	18.2		
Chewable Tablet	16.3	- 17.4	-2.3
T_{max} (hours)			
Caplet	1.49		
Chewable Tablet	1.81	2.4	44.9

[1]$AUC_{0\text{-}LOQ}$ and C_{max} variables presented as backtransformed geometric means, T_{max} presented as least squares mean.
[2]Confidence Interval = the percentage by which the lower and upper bounds of the 90% confidence interval based on the difference in the mean of the chewable tablet formulation minus the mean of the caplet formulation lie from the caplet formulation reference mean.

Table 2. Means and Confidence Intervals: 75 mg Carprofen Caplet and 75 mg Carprofen Chewable Tablet (Phase II, 3.0 mg/lb Dosing)

Pharmacokinetic Variable	Mean[1]	90% Confidence Interval[2] Lower Bound (%)	Upper Bound (%)
$AUC_{0\text{-}LOQ}$ (μg/mL●hr)			
Caplet	347.2		
Chewable Tablet	311.1	-31.6	18.4
C_{max} (μg/mL)			
Caplet	41.7		
Chewable Tablet	41.3	-25.6	27.8
T_{max} (hours)			
Caplet	1.94		
Chewable Tablet	1.44	-63.1	11.5

[1]$AUC_{0\text{-}LOQ}$ and C_{max} variables presented as backtransformed geometric means, T_{max} presented as least squares mean.
[2]Confidence Interval = the percentage by which the lower and upper bounds of the 90% confidence interval based on the difference in the mean of the chewable tablet formulation minus the mean of the caplet formulation lie from the caplet formulation reference mean.

The area under the curve ($AUC_{0\text{-}LOQ}$), C_{max} and T_{max} were highly similar between the 25 mg dose strengths of each formulation. Ninety percent confidence intervals applied to log transformed data for $AUC_{0\text{-}LOQ}$ and C_{max} for the chewable tablet were within ± 20% of the mean of the caplet for the 25 mg strength but not the 75 mg. strength. For the T_{max} variable, the 90% confidence intervals bounded zero for both dose strengths.

In Phase I, there were no significant ($P > 0.05$) differences between geometric mean plasma concentrations of carprofen administered as a 25 mg caplet versus as a 25 mg chewable tablet at any time point. Similarly, in Phase II, there were no significant ($P > 0.05$) differences between geometric mean plasma concentrations of carprofen administered as a 75 mg caplet versus as a 75 mg chewable tablet at any time point.

e. Statistical Methods: The data were analyzed with a mixed model procedure (SAS/STAT User's Guide, SAS Institute, Cary, North Carolina). Three pharmacological variables [area under curve ($AUC_{0\text{-}LOQ}$, μg/mL•hr), maximum concentration (C_{max}, μg/mL) and time at

maximum concentration (T_{max}, hours)] were calculated for each animal treatment combination. For each of these pharmacological variables the mixed model procedure partitioned the total sum of squares into sources appropriate for the design and estimated the treatment means and their standard deviations. Using the treatment means and their standard deviations, ninety per cent (90%) confidence intervals for the difference between the chewable tablet and the caplet, relative to the caplet, were calculated. The $AUC_{0\text{-}LOQ}$ and C_{max} variables were transformed to the natural log before analysis and the treatment least squares means were backtransformed to geometric means.

f. Suspected Adverse Events: Animals remained healthy for the duration of the study. Two single incidents of abnormal gastrointestinal signs were noted in two dogs (one episode of vomiting and one episode of soft stool occurring within 48 hours and 6 days of dosing, respectively). Abnormal clinical signs were self-limiting and resolved without veterinary care.

g. Conclusions: The area under the time-concentration curve ($AUC_{0\text{-}LOQ}$) and maximum serum carprofen concentration (C_{max}) are statistically equivalent between carprofen 25 mg caplets and 25 mg chewable tablets. The area under the time-concentration curve ($AUC_{0\text{-}LOQ}$) and maximum serum carprofen concentration (C_{max}) were not statistically equivalent between carprofen 75 mg caplets and 75 mg chewable tablets. These data confirm equivalent drug bioavailability between the two formulations for the 25 mg concentration and not the 75 mg concentration.

2. Bioavailability of 75 mg caplets and 75 mg chewable tablets (Study # 2567-60-98-090)

a. Type of Study: Relative Bioavailability

b. Investigator: Dr. Elizabeth I. Evans
Midwest Research Institute (MRI)
45 Volker Boulevard
Kansas City, Missouri

c. General Design:

i. Purpose: The objective of this study was to demonstrate comparable relative bioavailability between single doses of 75 mg of carprofen in a caplet formulation and single doses of 75 mg of carprofen in a chewable tablet formulation. This study was conducted as a follow-up study due to the failure to show comparable bioavailability between

the 75 mg caplet formulation and the chewable formulation in Phase II of Study # 2567A-60-97-106.

ii. Test Animals: 20 healthy male Beagle dogs approximately 8-9 months of age and ranging in weight from 20.8-31.1 lb were selected for the study.

iii. Control Group: Rimadyl® caplets (75 mg)

iv. Dosage Form: Rimadyl® chewable tablets (75 mg) and the proposed market chewable formulation of Rimadyl.

v. Route of Administration: Oral

vi. Dose: 3.0 mg/lb of carprofen as 75 mg caplet and 75 mg chewable tablet.

vii. Study Design: The study was a two-period, two treatment crossover experimental design, with each replicate being separated by a washout period of 10 days. Dogs were randomly assigned to two groups (A or B) of 10 dogs each and dosed with approximately 3.0 mg/lb of carprofen as a 75 mg caplet or a 75 mg chewable tablet.

viii. Parameters measured: Plasma samples were collected for carprofen analyses prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 ,24, 36, and 48 hours following dosing. Plasma samples were assayed for carprofen using a validated HPLC method.

d. Results: Means and confidence interval boundary information for the pharmacokinetic variables (AUC_{LOQ}, C_{max}, and T_{max}) are summarized in Table 1.

Table 1. Means and Confidence Intervals: 75 mg Carprofen Caplet and 75 mg Carprofen Chewable Tablet (Phase II, 3.0 mg/lb Dosing)

Pharmacokinetic Variable	Mean[1]	90% Confidence Interval[2] Lower Bound (%)	Upper Bound (%)
$AUC_{0\text{-}LOQ}$ (µg/mL•hr)			
Caplet	381.2[a]		
Chewable Tablet	382.0[a]	-5.9	6.8
C_{max} (µg/mL)			
Caplet	44.5[a]		
Chewable Tablet	44.0[a]	-11.1	10.1
T_{max} (hours)			
Caplet	1.48[a]		
Chewable Tablet	2.23[b]	25.5	76.2

[1] $AUC_{0\text{-}LOQ}$ and C_{max} variables presented as back-transformed geometric means, T_{max} presented as least squares mean.
[2] Confidence Interval = the percentage by which the lower and upper bounds of the 90% confidence interval based on the difference in the mean of the chewable tablet formulation minus the mean of the caplet formulation lie from the caplet formulation reference mean.
[a,b] Means within pharmacological variables with unlike superscripts are significantly ($P \leq 0.05$) different.

There were no significant ($P > 0.05$) differences between the 75 mg caplet and chewable tablet formulations for the area under the curve ($AUC_{0\text{-}LOQ}$) and maximum plasma carprofen concentration (C_{max}) variables. Ninety percent confidence intervals applied to log transformed data for $AUC_{0\text{-}LOQ}$ and C_{max} for the chewable tablet were within ± 20% of the mean of the caplet for the 75 mg strength. These data confirm equivalent drug bioavailability between the two formulations as administered.

e. Statistical Methods: The data were analyzed with a mixed model procedure (SAS/STAT User's Guide, SAS Institute, Cary, North Carolina). Three pharmacological variables [area under curve ($AUC_{0\text{-}LOQ}$, µg/mL•hr), maximum concentration (C_{max}, µg/mL) and time at maximum concentration (T_{max}, hours)] were calculated for each animal treatment combination. For each of these pharmacological variables the mixed model procedure partitioned the total sum of squares into sources appropriate for the design and estimated the treatment means and their standard deviations. Using the treatment means and their standard deviations, ninety per cent (90%) confidence intervals for the difference

between the chewable tablet and the caplet, relative to the caplet, were calculated. The $AUC_{0\text{-}LOQ}$ and C_{max} variables were transformed to the natural log before analysis and the treatment least squares means were backtransformed to geometric means.

f. Suspected adverse events: Animals remained healthy for the duration of the study. Two single incidents of abnormal gastrointestinal signs were noted in two dogs (one episode of vomiting after consumption of bandage material and one episode of loose stool which occurred within 8 hours and 36 hours after dosing, respectively). A third dog was noted to have superficial carpal lesions at approximately 24 hours after dosing, likely due to self-induced trauma from rubbing and /or catheter tape. Abnormal clinical signs were self-limiting and resolved without veterinary care.

g. Conclusions: Based on confidence intervals, the $AUC_{0\text{-}LOQ}$ and the C_{max} were equivalent between the 75 mg carprofen caplet and chewable tablet formulations. These data confirm equivalent drug bioavailability between the two formulations at the 75 mg dosage strength.

3. Palatability of twice-daily chewable tablets containing 25 mg or 100 mg of carprofen. (Study No. 2767A-60-97-105).

a. Type of Study: Palatability

b. Investigator: Dr. David R. Young
Young Veterinary Research Services
Turlock, California

c. General Design:

i. Purpose: The objective of this study was to demonstrate in small and large dogs the palatability of twice-daily chewable tablet formulations containing either 25 mg carprofen (for small dogs) or 100 mg carprofen (for large dogs) compared to the same formulation containing no drug.

ii. Test Animals: Thirty (30) adult mixed breed and purebred dogs (15 small dogs and 15 large dogs) of mixed sexes and ranging in age from 2 to 8 years participated in the study.

iii. Control Group: Placebo (same as Rimadyl® chewable tablet formulation with the omission of the active ingredient).

iv. Dosage Form: Rimadyl® chewable tablets (25 mg and 100 mg). The chewable tablets administered were the same as the proposed market formulation.

v. Route of Administration: Oral

vi. Dose: 25 mg to small dogs (8.3-16.9 kg) and 100 mg to large dogs (23.4-34.7 kg) twice daily for 14 days. Placebo: 0 mg of carprofen twice daily for 14 days.

vii. Study Design: On Days -3 to -1, each dog was pre-conditioned to a two position palatability testing rack and testing procedures by offering commercially available dog treats in each of the two test positions. From Day 0 through Day 13, dogs were offered the two chewable tablet formulations twice daily (morning and afternoon) via the testing rack. Small dogs were offered tablets containing 25 mg carprofen (Tablet A) or no drug (Tablet B), while large dogs were offered tablets containing 100 mg carprofen (Tablet C) or no drug (Tablet D). Food was removed at least two hours prior to morning testing and was not available until completion of the afternoon testing. The position location for each tablet on each day (both morning and afternoon) was randomly determined with the restriction that each formulation (placebo or active) was offered in each position of the rack an equal number of times during the study period.

viii. Parameters measured: An observer blinded to treatment determined if a dog consumed a tablet. A tablet was not considered consumed until it was completely swallowed. A Yes or No consumption score was recorded for each tablet for each dog. Five minutes was allowed for each palatability test. Dogs were observed twice daily for adverse reactions and for general physical health.

d. Results: 27 of the 30 dogs consumed every tablet offered at every trial. This gives a 95% confidence interval of (73.5%, 97.9%) for the percentage of dogs in the target population who are likely to consume every tablet offered on repeated trials. One dog refused both tablets on only one trial but consumed both tablets for the other 27 trials. Two dogs refused both tablets on 13 of the 28 trials. Of these two dogs, one ate only the drug tablet on two of the trials, ate only the placebo tablet on one of the trials, and consumed both tablets on the remaining 12 trials. The other dog ate only the placebo tablet on one of the other trials, and consumed both tablets on the remaining 14 trials.

e. Statistical Methods: The data from the small and large dogs were pooled. The dog was considered to be the independent experimental unit of the

analysis, and 95% confidence intervals were calculated from exact procedures for the percentage of dogs in the target population that could be expected to consume all tablets on repeated trials.

f. Suspected adverse events: Vomitus or material possibly representing vomitus was observed in the runs of two dogs during palatability testing. Soft feces was observed in the runs of four dogs during palatability testing. One of these dogs was also reported to be depressed on one of the days soft feces was noted. These clinical signs were mild, self-limiting and resolved without veterinary care. In general, dogs remained healthy throughout the study and maintained their body weight.

g. Conclusions: Carprofen as a 25 mg chewable tablet (for small dogs) and carprofen as a 100 mg chewable tablet (for large dogs) was highly palatable and well tolerated by both weight classes of dogs.

4. Relative dissolution of 25, 75 and 100 mg dose strengths of carprofen in caplet and chewable tablet formulations (Study No.: 2567A-60-97-137).

a. Type of study: *In vitro* dissolution

b. Investigator: Ronald G. Holtgrewe
Pfizer Animal Health
601 W. Cornhusker Hwy.
Lincoln, Nebraska

c. General Design

i. Purpose: The objective of the study was to demonstrate dissolution profiles of 25, 75 and 100 mg dose strengths of the carprofen chewable tablet formulation and the equivalent dose strengths of the carprofen caplet formulation. These dissolution data support the approval of the 100 mg chewable tablet.

ii. Control Group: Rimadyl® caplets (25 mg, 75 mg and 100 mg). The caplets were the same as the commercially marketed formulation.

iii. Dosage Form: Rimadyl® chewable tablets (25 mg, 75 mg and 100 mg). The chewable tablets were the same as the proposed market formulation.

iv. Study Design: Two identical dissolution apparatuses (USP apparatus 2) were used, one for the chewable tablets and one for the caplets. Six chewable tablets and six caplets (two of each dose strength) were tested daily. The dissolution media consisted of USP simulated intestinal fluid

without enzymes, pH 7.5. Dissolution of the chewable tablets was performed at 100 rpm for 120 minutes with samples collected at seven time periods (5, 15, 30, 45, 60, 90 and 120 minutes). There was no attempt to break or pulverize chewable tablets prior to addition to the dissolution media. Carprofen caplets were tested at 50 rpm for 30 minutes, with samples collected at three time periods (5, 15 and 30 minutes).

v. Parameters Measured: Carprofen content of each chewable tablet sample was determined by high performance liquid chromatography (HPLC). Carprofen content of each caplet sample was determined by measuring spectrophotometric absorbance. The percent of drug released from each dose strength for each formulation was calculated at each timepoint.

d. Results:

Although the *in vitro* dissolution rate for the chewable tablets was significantly slower than that of the caplets, both formulations succeeded in demonstrating greater than 87% dissolution by the end of the respective sampling periods (see Tables 6 and 7). The mean percent release at 30 minutes for the 25 mg and 100 mg caplet formulations were 97.0% and 93.4% respectively, a difference of approximately 3.6%. The mean percent release at 120 minutes for the 25 mg and 100 mg chewable tablets were 91.4% and 88.3% respectively, a difference of approximately 3.1%.

There were significant differences ($P \leq 0.05$) in the percent release between the 25 mg and 75 mg caplets and 25 and 100 mg caplets at all three sampling times (5, 15 and 30 minutes). There were also significant differences ($P \leq 0.05$) between the 75 mg and 100 mg caplets at 5 and 15 minutes, but not ($P > 0.05$) at 30 minutes.

Table 6. Mean Percent Carprofen Release - Caplets

	Time (minutes)		
Dose	5	15	30
25 mg	85.9	94.7	97.0
75 mg	59.1	88.7	94.6
100 mg	77.2	91.0	93.4
Contrast			
25 mg vs. 75	*	*	*
25 mg vs.	*	*	*
75 mg vs.	*	*	ns

* = significant difference ($P \leq 0.05$) ns = no significant difference ($P > 0.05$)

There were no significant differences ($P > 0.05$) in percent release between the 25 mg and 75 mg chewable tablets and 25 mg and 100 mg chewable tablets at 5 minutes. There were significant differences ($P \leq 0.05$) at all other sampling times (15, 30, 45, 60, 90 and 120 minutes). There were no significant differences ($P > 0.05$) between the 75 mg and 100 mg chewable tablet at any sampling time.

Table 7. Mean Percent Carprofen Release - Chewable Tablets

	Time (minutes)						
Dose Strength	5	15	30	45	60	90	120
25 mg							
75 mg	12.9	34.3	53.2	64.3	73.5	84.8	87.1
100 mg	12.7	35.3	54.2	64.6	73.0	86.3	88.3
Contrast							
25 mg vs. 75	ns	*	*	*	*	*	*
25 mg vs 100	ns	*	*	*	*	*	*
75 mg vs 100	ns	ns	ns	ns	ns	ns	ns

* = significant difference ($P \leq 0.05$) ns = no significant difference ($P > 0.05$)

* = significant difference ($P \leq 0.05$) ns = no significant difference ($P > 0.05$)

In addition, the f2 factor, based upon the comparative profiles of the 75 mg and 100 mg chewable tablets, was 97. This value is contained within the limits of 50 to 100, indicating that the two dissolution profiles are comparable.

e. Statistical Methods:

The data were analyzed with a mixed model procedure (SAS/STAT User's Guide, SAS Institute, Cary, North Carolina). The response variable (percent carprofen released) was analyzed using a multivariate, repeated measures approach to assess the effect of dosage strength and sampling time (the fixed effects). The variability attributable to block (day during which the dissolution was conducted) was treated as a random variable. One degree of freedom contrasts between treatments (dose strengths) at each time period were made. The analysis was carried out separately for the two formulations.

Since the 75 mg chewable tablets was shown to be bioequivalent to the 75 mg caplet formulation, additional support of the waiver request for the 100 mg chewable tablets was obtained by estimating the f2 factor, thereby confirming the similarity in the profiles for the 75 mg and 100

mg chewable tablets. This model-independent metric is estimated as follows:

$$f2 = 50 * \log\{[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)]^{-0.5} * 100\}$$

where n = number of time points
R_t = dissolution value of the reference batch at time t
T_t = the dissolution value of the test batch at time t.

For curves to be considered similar, f2 values should range between 50-100.

f. Conclusions:

Waiver of *in vivo* bioequivalence study requirements for the 100 mg chewable tablets is granted on the basis of the following information: the lack of significant differences between the percent carprofen dissolved from the 75 mg and 100 mg caplet formulations, the similarity in the *in vitro* dissolution profiles of the 75 mg and 100 mg chewable tablets, and the successful demonstration of *in vivo* product bioequivalence for the 75 mg chewable tablet and the 75 mg caplet formulation. Accordingly, the 100 mg chewable tablets and 100 mg caplets are determined to be bioequivalent.

V. Animal Safety:

Studies demonstrating the safety of Rimadyl® chewable tablets for use in dogs is contained in the FOI Summary for the approval for Rimadyl® caplets under NADA 141-053. No further studies were conducted with Rimadyl® chewable tablets.

VI. Human Safety:

Human Safety Relative to Food Consumption:

Data on human food safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. Rimadyl® chewable tablets are approved for use in dogs only.

Human Safety Relative to Possession, Handling and Administration:

Labeling contains adequate caution/warning statements.

VII. Agency Conclusions:

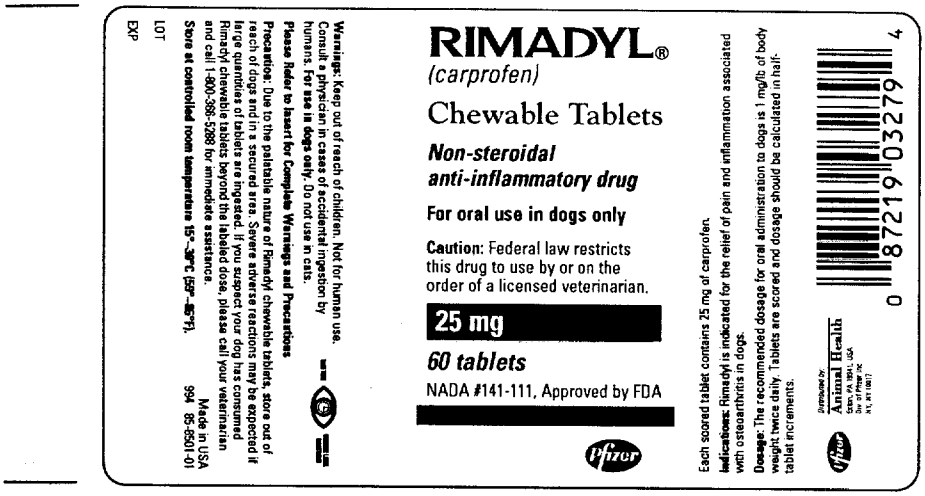
Data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. Its demonstrates that Rimadyl® chewable tablets (carprofen), when used under labeled conditions of use, are safe and effective.

Rimadyl® chewable tablets are restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine when a dog has osteoarthritis which is clinically severe enough to warrant treatment with such a non-steroidal anti-inflammatory drug.

Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval for non food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

Labeling:

Package Insert
Carton Label
Bottle Label



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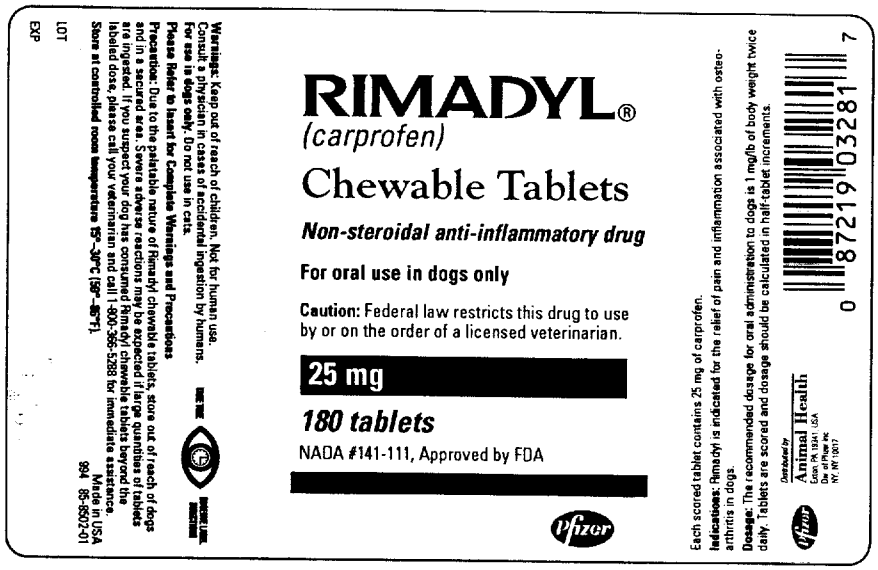
PMS 116	PMS 330	PMS 286	Black	Pattern Varnish

85-8501-01 Facsimile Draft #1 4/27/99



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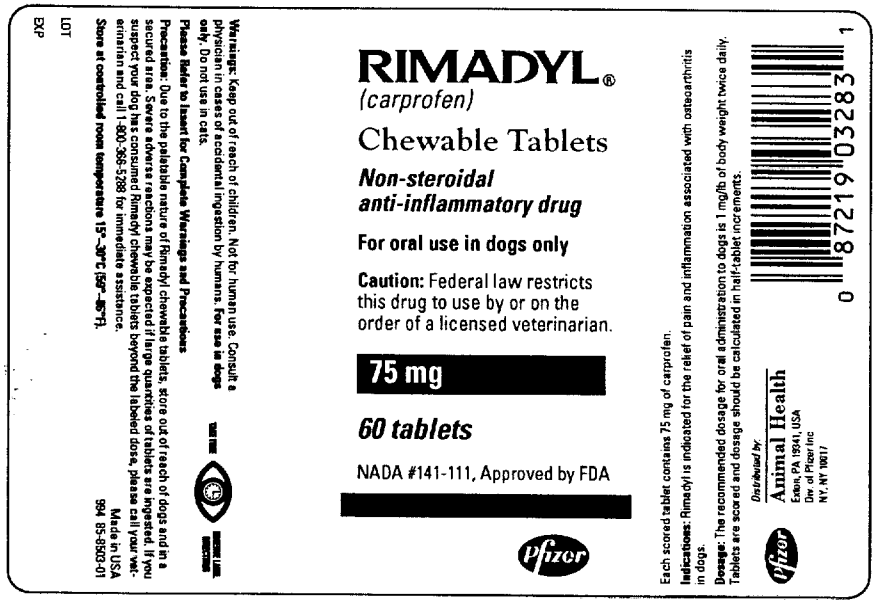
85-8502-01 Facsimile Draft #1 4/27/99



4 1/2" (W) X 3 1/16" (H)

PMS 116	PMS 330	PMS Rhodamine Red	Black	Pattern Varnish

85-8503-01 Facsimile Draft #1 4/27/99

RIMADYL®
(carprofen)

Chewable Tablets

Non-steroidal anti-inflammatory drug

For oral use in dogs only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

75 mg

180 tablets

NADA #141-111, Approved by FDA

Pfizer

Each scored tablet contains 75 mg of carprofen.

Indications: Rimadyl is indicated for the relief of pain and inflammation associated with osteoarthritis in dogs.

Dosage: The recommended dosage for oral administration to dogs is 1 mg/lb of body weight twice daily. Tablets are scored and dosage should be calculated in half-tablet increments.

Distributed by
Pfizer Animal Health
Exton, PA 19341, USA
Div. of Pfizer Inc.
NY, NY 10017

0 87219 03285 5

Warnings: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats.

Please Refer to Insert for Complete Warnings and Precautions

Precaution: Due to the palatable nature of Rimadyl chewable tablets, store out of reach of dogs and in a secured area. Severe adverse reactions may be expected if large quantities of tablets are ingested. If you suspect your dog has consumed Rimadyl chewable tablets beyond the labeled dose, please call your veterinarian and call 1-800-366-5288 for immediate assistance.

Store at controlled room temperature 15°–30°C (59°–86°F).

Made in USA

994 85-8504-01

LOT

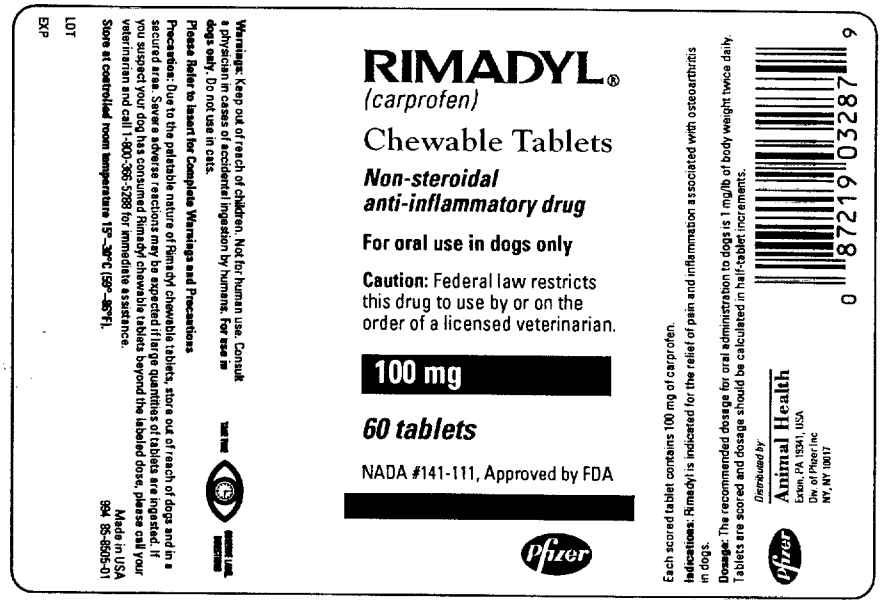
EXP

READ THE ENTIRE LABEL BEFORE USING

7 1/2" (W) X 3" (H)

PMS 116	PMS 330	PMS Rhodamine Red	Black	Pattern Varnish

85-8504-01 Facsimile Draft #1 4/27/99



4 1/2" (W) X 3 1/16" (H)

PMS 116	PMS 330	PMS 3275	Black	Pattern Varnish

85-8505-01 Facsimile Draft #1 4/27/99

RIMADYL®
(carprofen)

Chewable Tablets

Non-steroidal anti-inflammatory drug

For oral use in dogs only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

100 mg

180 tablets

NADA #141-111, Approved by FDA

Pfizer

Each scored tablet contains 100 mg of carprofen.

Indications: Rimadyl is indicated for the relief of pain and inflammation associated with osteoarthritis in dogs.

Dosage: The recommended dosage for oral administration to dogs is 1 mg/lb of body weight twice daily. Tablets are scored and dosage should be calculated in half-tablet increments.

Distributed by:
Animal Health
Easton, PA 18041, USA
Div. of Pfizer Inc
NY, NY 10017

0 87219 03289 3

Warnings: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats.

Please Refer to Insert for Complete Warnings and Precautions

Precaution: Due to the palatable nature of Rimadyl chewable tablets, store out of reach of dogs and in a secured area. Severe adverse reactions may be expected if large quantities of tablets are ingested. If you suspect your dog has consumed Rimadyl chewable tablets beyond the labeled dose, please call your veterinarian and call 1-800-366-5288 for immediate assistance.

Store at controlled room temperature 15°–30°C (59°–86°F). 994 85-8506-01

Made in USA

LOT

EXP

7 1/2" (W) X 3 1/2" (H)

PMS 116 | PMS 330 | PMS 3275 | Black | Pattern Varnish

85-8506-01 Facsimile Draft #1 4/27/99

RIMADYL®
(carprofen)

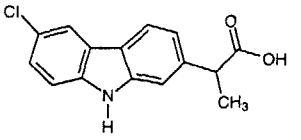
Chewable Tablets

Non-steroidal anti-inflammatory drug

For oral use in dogs only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Rimadyl (carprofen) is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. The chemical name for Rimadyl, a substituted carbazole, is (±)-6-chloro-α-methylcarbazole-2-acetic acid and its structural formula is:



Carprofen is a white, crystalline compound with an empirical formula of $C_{15}H_{12}NO_2Cl$ and a molecular weight of 273.72. It is freely soluble in ethanol, but practically insoluble in water at 25°C.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent to indomethacin in animal models.[1]

As with other NSAIDs, the exact mode of action of carprofen has not been established; however, inhibition of prostaglandin synthesis accounts for at least part of its mode of action. Carprofen is a reversible inhibitor of cyclo-oxygenase and a moderately potent inhibitor of phospholipase A_2. Carprofen has also been shown to inhibit the release of several prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating inhibition of acute (PMN system) and chronic (synovial cell system) inflammatory reactions.[1]

In rats, carprofen has been shown to be a much weaker blocker of arachidonic acid-induced diarrhea than indomethacin.[2] This decreased effect of carprofen on prostaglandin synthesis in the gastrointestinal tract may explain its relatively low ulcerogenic activity compared to other drugs in its class.[1]

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses.[3–7] Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF), PGE_1, and PGE_2 by its inhibitory effect in prostaglandin biosynthesis.[1]

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally.[8] Peak blood plasma concentrations are achieved in 1–3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5–9.8 hours) after single oral doses varying from 1–35 mg/kg of body weight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog. Rimadyl is more than 99% bound to plasma protein and exhibits a very small volume of distribution.

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70–80%) and urine (10–20%). Some enterohepatic circulation of the drug is observed.

INDICATIONS: Rimadyl is indicated for the relief of pain and inflammation associated with osteoarthritis in dogs.

DOSAGE AND ADMINISTRATION: The recommended dosage for oral administration to dogs is 1 mg/lb of body weight twice daily. Rimadyl chewable tablets are scored and dosage should be calculated in half-tablet increments. Tablets can be halved by placing the tablet on a hard surface and pressing down on both sides of the score. Rimadyl chewable tablets are palatable and willingly consumed by most dogs when offered by the owner. Therefore, they may be fed by hand or placed on food. Care should be taken to ensure that the dog consumes the complete dose.

PALATABILITY: A controlled palatability study was conducted which demonstrated that Rimadyl chewable tablets were readily accepted and consumed on first offering by a majority of dogs.

SAFETY: Laboratory studies and clinical field trials have demonstrated that Rimadyl is well tolerated in dogs after oral administration.

In target animal safety studies, Rimadyl was administered to dogs at 1, 3, and 5 times the recommended dose for 42 consecutive days with no significant adverse reactions. Serum albumin for a single female dog receiving 5 times the recommended dose decreased to 2.1 g/dL after 2 weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2.3 g/dL at the final 6-week evaluation. Over the 6-week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with the recommended dose and in 1 dog (2 incidents) treated with 3 times the recommended dose. Redness of the colonic mucosa was observed in 1 male that received 3 times the recommended dose.

Two of 8 dogs receiving 10 times the recommended dose (10 mg/lb twice daily) for 14 days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination. Histologic examination of these areas revealed no evidence of ulceration, but did show minimal congestion of the lamina propria in 2 of the 5 dogs.

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered up to 11.4 mg/lb/day (5.7 times the recommended total daily dose) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No gross or histologic changes were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU.

In the 52 week study, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 297 dogs of different breeds at the recommended dose for 14 days. The drug was clinically well tolerated and the incidence of clinical adverse reactions for Rimadyl-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in Rimadyl). Mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving Rimadyl and placebo, respectively. Differences were not statistically significant. Changes in clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant nor reported as adverse reactions. The recommended course of therapy was repeated as needed at 2-week intervals in 244 of the dogs, some for as long as 5 years.

CONTRAINDICATIONS: Rimadyl should not be used in dogs exhibiting previous hypersensitivity to carprofen.

PRECAUTIONS: As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclo-oxygenase which is responsible for the formation of prostaglandins from arachidonic acid.[9–12] When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients.[10,12] NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy.[9–12]

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of Rimadyl with other anti-inflammatory drugs, such as corticosteroids and NSAIDs, should be avoided or very closely monitored. Sensitivity to drug-associated adverse reactions varies with the individual patient. For example, Rimadyl

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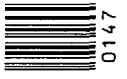

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treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in dogs.

Rimadyl is not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of Rimadyl in pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Studies to determine the activity of Rimadyl when administered concomitantly with other protein-bound drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy.

Due to the palatable nature of Rimadyl chewable tablets, store out of reach of dogs in a secured location. Severe adverse reactions may occur if large quantities of tablets are ingested. If you suspect your dog has consumed Rimadyl chewable tablets above the labeled dose, please call your veterinarian for immediate assistance and notify Pfizer Animal Health (1-800-366-5288).

INFORMATION FOR DOG OWNERS:
Rimadyl, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include decreased appetite, vomiting, diarrhea, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue Rimadyl therapy and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

WARNINGS: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats.

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. **Owners should be advised to observe for signs of potential drug toxicity (see Information for Dog Owners and Adverse Reactions).**

ADVERSE REACTIONS: During investigational studies for the caplet formulation, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen caplet- and placebo-treated dogs. Incidences of the following were observed in both groups: vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%). The product vehicle served as control.

During investigational studies for the chewable tablet formulation, gastrointestinal signs were observed in some dogs. These signs included vomiting and soft stools.

Post-Approval Experience:
Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: *Vomiting, diarrhea, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.*

Hepatic: *Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, hyperbilirubinuria, hypoalbuminemia. Approximately one-fourth of hepatic reports were in Labrador Retrievers.*

Neurologic: *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation.*

Urinary: *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities including acute tubular necrosis, renal tubular acidosis, glucosuria.*

Behavioral: *Sedation, lethargy, hyperactivity, restlessness, aggressiveness.*

Hematologic: *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis.*

Immunologic or hypersensitivity: *Facial swelling, hives, erythema.*

In rare situations, death has been associated with some of the adverse reactions listed above.

To report a suspected adverse reaction call 1-800-366-5288.

STORAGE: Store at controlled room temperature 15°–30°C (59°–86°F).

HOW SUPPLIED: Rimadyl chewable tablets are scored, and contain 25 mg, 75 mg, or 100 mg of carprofen per tablet. Each tablet size is packaged in bottles containing 60 or 180 tablets.

REFERENCES:

1. Baruth H, *et al:* In Anti-Inflammatory and Anti-Rheumatic Drugs, Vol. II, Newer Anti-Inflammatory Drugs, Rainsford KD, ed. CRC Press, Boca Raton, p. 33, 1986.
2. Strub KM, *et al:* Relation between ulcerogenic activity of various NSAID and their potency as inhibitors of prostaglandin synthesis *in vivo*. In Arachidonic Acid Metabolism in Inflammation and Thrombosis. Brune K, Baggiolini M, eds. Birkhauser Verlag, Basel, p. 245, 1979.
3. Ceuppens JL, *et al:* Non-steroidal anti-inflammatory agents inhibit the synthesis of IgM rheumatoid factor *in vitro*. *Lancet* 1:528, 1982.
4. Ceuppens JL, *et al:* Endogenous prostaglandin E_2 enhances polyclonal immunoglobulin production by ionically inhibiting T suppressor cell activity. *Cell Immunol* 70:41, 1982.
5. Schleimer RP, *et al:* The effects of prostaglandin synthesis inhibition on the immune response. *Immunopharmacology* 3:205, 1981.
6. Leung KH, *et al:* Modulation of the development of cell mediated immunity: Possible roles of the products of cyclo-oxygenase and lipoxygenase pathways of arachidonic acid metabolism. *Int J Immunopharmacology* 4:195, 1982.
7. Veit BC: Immunoregulatory activity of cultured-induced suppressor macrophages. *Cell Immunol* 72:14, 1982.
8. Schmitt M, *et al:* Biopharmaceutical evaluation of carprofen following single intravenous, oral, and rectal doses in dogs. *Biopharm Drug Dispos* 11(7):585, 1990.
9. Kore AM: Toxicology of nonsteriodal anti-inflammatory drugs. Veterinary Clinics of North America, *Small Animal Practice* 20, March 1990.
10. Binns SH: Pathogenesis and pathophysiology of ischemic injury in cases of acute renal failure. *Compend for Cont Ed* 16:1, January 1994.
11. Boothe DM: Prostaglandins: Physiology and clinical implications. *Compend for Cont Ed* 6:11, November 1984.
12. Rubin SI: Nonsteroidal anti-inflammatory drugs, prostaglandins, and the kidney. *JAVMA* 188:9, May 1986.

For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Pfizer Animal Health at 1-800-366-5288.

NADA #141-111, Approved by FDA

TAKE TIME OBSERVE LABEL DIRECTIONS

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